DEVELOPMENT OF DRUGS TARGETING THE PI3K SIGNALLING PATHWAY IN LEUKAEMIAS AND LYMPHOMAS

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ABSTRACT

The phosphoinositide 3-kinase (PI3K) family of signalling enzymes play a key role in the transduction of signals from activated cell surface receptors controlling cell growth and proliferation, survival, metabolism, and migration. The intracellular signalling pathway from activated receptors to PI3K and its downstream targets v-akt murine thymoma viral oncogene homolog (Akt) and mechanistic target of rapamycin (mTOR) is very frequently deregulated by genetic and epigenetic mechanisms in human cancer, including leukaemia and lymphoma. In the past decade, an arsenal of small molecule inhibitors of key enzymes in this pathway has been developed and evaluated in pre-clinical studies and clinical trials in cancer patients. These include pharmacological inhibitors of Akt, mTOR, and PI3K, some of which are approved for the treatment of leukaemia and lymphoma. The PI3K family comprises eight different catalytic isoforms in humans, which have been subdivided into three classes. Class I PI3K isoforms have been extensively studied in the context of human cancer, and the isoforms p110α and p110δ are validated drug targets. The recent approval of a p110δ-specific PI3K inhibitor (idelalisib/Zydelig®) for the treatment of selected B cell malignancies represents the first success in developing these molecules into anti-cancer drugs. In addition to PI3K inhibitors, mTOR inhibitors are intensively studied in leukaemia and lymphoma, and temsirolimus (Torisel®) is approved for the treatment of a type of lymphoma. Based on these promising results it is hoped that additional novel PI3K pathway inhibitors will in the near future be further developed into new drugs for leukaemia and lymphoma.

Keywords: Akt, B cell receptor, leukaemia, lymphoma, mTOR, phosphoinositide 3-kinase, PTEN.

INTRODUCTION

Leukaemia and Lymphoma

Leukaemia represents 3% of new cancer cases in males and females, while lymphoma represents 5% and 4% of new cases in males and females, respectively.[1] In terms of deaths, leukaemia accounts for 4% and 3% of total cancer deaths in males and females, respectively, while lymphoma accounts for 3% in both sexes.[1] Leukaemia is subdivided into acute lymphocytic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), and chronic myeloid leukaemia (CML), for which different therapies are used and outcomes vary.[2] Two main categories of lymphoma are Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), the latter making up around 90% of cases.[3] However, lymphomas are currently classified depending on cell type, of which several types exist.[4,5] The 2008 World Health Organization classification categorises the tumours of the haematopoietic and lymphoid tissues into: (i) mature B cell neoplasms; (ii) mature T cell and natural killer cell neoplasms; (iii) HL; (iv) histiocytic and dendritic cell neoplasms; and (v) post-transplant lymphoproliferative disorders.[4,5] The management of haematological malignancies such as leukaemia and lymphoma has greatly benefited from the development of targeted anti-cancer therapies in the past decade.[6,7] Successful

examples of targeted therapies include anti-CD20 monoclonal antibodies (rituximab) in ALL and B cell lymphoma.[7] Small molecule inhibitors (imatinib, Glivec®/Gleevec®) of the BCR-ABL kinase (breakpoint cluster region-Abelson murine leukaemia viral oncogene homolog) have been successfully applied to the treatment of CML. The hyper-activation of the phosphoinositide 3-kinase/v-akt murine thymoma viral oncogene homolog/mechanistic target of rapamycin (PI3K/Akt/mTOR) pathway has been linked to increased cell growth and proliferation, survival, and chemoresistance in leukaemia and lymphoma, and thus also represents an attractive target for the development of anti-cancer drugs in these malignancies.[8-12]

The PI3K Signalling Pathway

PI3Ks are a family of lipid kinases that catalyse the phosphorylation of plasma membrane phosphoinositides on the D-3 position of the inositol ring, resulting in the production of three distinct second messengers: phosphatidylinositol 3-monophosphate (PI(3)P), phosphatidylinositol 3,4-bisphosphate (PI(3,4)P_2), and phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P_3/PIP_3).[13] PIP_3 is the key second messenger in the activation of the PI3K downstream targets Akt and mTOR. In short, PIP_3 binding to the pleckstrin homology domains of Akt and phosphoinositide-dependent protein kinase-1 (PDK1) results in full activation of Akt, through phosphorylation at Thr308 by PDK1 and at Ser473 by the mechanistic target of rapamycin complex 2 (mTORC2) (Figure 1).[8,9,12] Active Akt then phosphorylates an array of proteins that control cell survival, growth, and cell cycle progression.[8,9,12] These include glycogen synthase kinase-3, forkhead box, subgroup O transcription factors, apoptosis-modulating proteins of the Bcl-2 family, and the murine double minute-2 E3 ubiquitin protein ligase (Figure 1).[8,9,12] Akt-mediated phosphorylation of the tuberous sclerosis-2 (TSC2) protein impairs the GTPase-activating activity of the TSC1/TSC2 complex towards the rat sarcoma (Ras) homologue enriched in the brain (Rheb). Rheb activates the mechanistic target of rapamycin complex 1 (mTORC1), which in turn controls cell growth via the ribosomal protein S6 kinase and eukaryotic translation initiation factor 4E binding protein (Figure 1).[8,9,12] Based on primary sequence homology, regulation, and *in vitro* substrate specificity, PI3Ks are subdivided into three classes (I-III).[12,14] Class I PI3Ks are further subdivided into Class I_A and I_B, based on the type of cell surface receptor that activates PI3Ks: Class I_A PI3Ks (comprising the catalytic isoforms p110α, p110β, and p110δ) are activated by receptor tyrosine kinases (*RTKs*), while the Class I_B PI3Ks (comprising the catalytic isoform p110γ) are activated by G protein-coupled receptors. Class I PI3Ks can also be activated by direct binding of Ras to the p110 catalytic isoforms.[8,9,12]

Deregulation of PI3K/Akt/mTOR Signalling in Cancer

Constitutive activation of the PI3K/Akt/mTOR pathway has been reported in many different human cancers and has been linked to different types of molecular alterations.[15] Somatic mutations can target the genes encoding catalytic PI3K isoforms (mostly *PIK3CA*-encoding p110α) or regulatory isoforms (mostly *PIK3R1*-encoding p85α). *PIK3CA* mutations are clustered in two 'hot spots' located in the helical (exon 9) and kinase (exon 20) domains and are associated with increased kinase activity and oncogenic potential.[16,17] Intriguingly, somatic mutations that activate catalytic Class I PI3K isoforms are mostly restricted to *PIK3CA*, and the genes encoding the other Class I catalytic isoforms, such as *PIK3CB*, *PIK3CD*, and *PIK3CG* have not been found to be targeted by the same 'hot spot' mutations in cancer.[16] However, it should be noted that p110β, p110δ, and p110γ have the ability to induce oncogenic transformation as wild-type proteins.[18] Somatic mutations found in cancer can also target the genes encoding Akt isoforms and mTOR. Another type of genetic alteration targeting components and regulators of the PI3K/Akt/mTOR pathway are mutations in the phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*).[15] PTEN is a phosphatase that de-phosphorylates PIP_3 to produce phosphatidylinositol 4,5-bisphosphate (PI(4,5)P_2), thus antagonising PI3K activity. *PTEN* regulation is complex and involves a variety of transcriptional and post-transcriptional events that can impact on its expression and activity.[19] In addition, the PI3K/Akt/mTOR pathway can be activated in cancer by mutations in *RTK* or *RAS* genes, *RTK* hyperactivation driven by receptor over-expression/amplification, or the establishment of autocrine loops involving RTKs and their cognate ligand.

PI3K/Akt/mTOR Signalling in Leukaemia and Lymphoma

Similarly to the situation in other cancers, deregulated activation of the PI3K/Akt/mTOR pathway has been reported in leukaemia and lymphoma.[9,11,12,20] In general, *PIK3CA* mutations are not believed to be the major cause of PI3K/Akt/mTOR pathway activation in leukaemia and lymphoma.[21] In contrast, *PTEN* inactivation has been reported in AML and NHL.[22,23] In addition, mutations and hyperactivation of tyrosine kinases (BCR-ABL), Feline McDonough Sarcoma-like tyrosine kinase 3, mast/stem cell growth factor receptor, platelet-derived growth factor receptor-β, or Ras (NRAS and KRAS), as well as increased expression/activity of components of the pathway can be the underlying factors.[8,9,24,25]

PI3K/Akt/mTOR Pathway Inhibitors as Anti-Cancer Drugs

Over 20 years after the discovery of the first pharmacological inhibitors of PI3K and mTOR, a wide array of small molecules has been developed by the pharmaceutical industry.[13,14,26,27] These can be broadly subdivided into different classes: pan-PI3K inhibitors (BKM-120), isoform-specific PI3K inhibitors (idelalisib, IPI-145), PI3K/mTOR inhibitors (BEZ-235, VS-5584), Akt inhibitors (MK-2206, perifosine), allosteric mTOR inhibitors (rapamycin analogs, rapalogs: sirolimus, everolimus, temsirolimus, ridaforolimus), and mTOR kinase inhibitors (OSI-027, CC-223) (Figure 1 and Figure 2). Generally, single agent PI3K/Akt/mTOR pathway inhibitor treatment has been reported to produce only incomplete responses in different cancers[27] and the genetic background of the tumours, in particular the *PIK3CA* mutational status, is believed to play a major role in the response to these agents.[28] However, combining these agents with standard chemotherapy or other targeted agents may represent a more promising approach to successful use of these agents in human cancer patients.[27]

PI3K/Akt/mTOR Pathway Inhibitors in Leukaemia and Lymphoma

In contrast to the situation in other cancers, B cell malignancies appear to be uniquely responsive to PI3K inhibitors, in particular to isoform-specific PI3K inhibitors targeting the Class I_A isoform p110δ.[14,27,29-31] This PI3K isoform is hallmarked by its tissue specificity, since it is mostly expressed in leukocytes and plays a crucial role in intracellular signalling by the B and T cell receptors.[32-34] Although it is not targeted by somatic mutations in cancer, its expression and activity was reported to be increased in leukaemia and linked to cell proliferation and chemoresistance.[14,35-37] Accordingly, small molecule inhibitors of p110δ (Figure 1 and Figure 2), in particular CAL-101 (idelalisib, Zydelig®) were shown to be active in several pre-clinical models of leukaemia and lymphoma.[14,36,38-41] The pre-clinical data for CAL-101 in leukaemia and lymphoma and the early phase clinical studies have been recently reviewed.[14,41] Pre-clinical studies of CAL-101 in CLL showed that the p110δ inhibitor induced apoptosis in primary cells *ex vivo*.[40] CAL-101 was also reported to induce apoptosis in lymphoma cell lines and primary cells.[38] The subsequent clinical trials with idelalisib led to its approval by the FDA in July 2014 for relapsed CLL (in combination with rituximab), for relapsed follicular B cell NHL, and for relapsed small lymphocytic leukaemia.[29,30,42] In a Phase I trial in relapsed/refractory CLL, idelalisib showed a favourable safety profile, while inducing an overall response rate (ORR) of 72%.[43] The Phase III study of idelalisib and rituximab in CLL patients demonstrated improved rates of overall response and overall survival at 12 months, compared to rituximab and placebo.[29] In a Phase I study in relapsed indolent NHL, idelalisib was reported to have a favourable safety profile and achieved an ORR of 47%.[44] Another Phase I study in relapsed/refractory mantle cell lymphoma also reported a favourable safety profile and an ORR of 40% for idelalisib.[45] The Phase II study of idelalisib in patients with NHL (follicular lymphoma, small lymphocytic lymphoma, marginal-zone lymphoma, and lymphoplasmacytic lymphoma with or without Waldenstrom's macroglobulinaemia), showed a response rate of 57%, with 6% of patients having complete responses.[30] Idelalisib also showed an acceptable safety profile in NHL patients in this study.[30] Idelalisib is currently undergoing further clinical testing in additional indications, as single agent or in combination with other drugs (Table 1).

In addition to CAL-101, other PI3K inhibitors are currently under study in leukaemia and lymphoma. IPI-145, a dual specificity p110δ and p110γ inhibitor, was shown to be active in pre-clinical studies in CLL.[46] This compound is currently being evaluated in clinical trials in lymphoma (Phase III in combination with rituximab) and CLL (Phase III in combination with the anti-CD20 monoclonal

antibody ofatumumab) (Table 1). BKM-120 is a pan-class I PI3K inhibitor which is currently undergoing clinical testing in different cancers. This inhibitor was reported to be active in pre-clinical studies in B cell lymphoma and CLL.[47-49] BKM-120 is currently undergoing Phase I and Phase II clinical testing in leukaemia and lymphoma (Table 1).

Another approach to target the PI3K/Akt/mTOR pathway in haematological cancers is to use dual specificity PI3K/mTOR inhibitors, such as BEZ-235 and VS-5584 (Figure 1 and Figure 2). BEZ-235 was reported to have pre-clinical activity in AML and lymphoma.[50-52] BEZ235 and VS-5584 are currently undergoing Phase I clinical testing in leukaemia (Table 1). The rapamycin analogs ('rapalogs') are allosteric inhibitors of mTOR and only inhibit mTORC1, while mTORC2 is resistant to these compounds. Rapalogs represent the class of inhibitors of the PI3K/Akt/mTOR pathway which are the subject of the greatest number of clinical trials at present (Table 1). The clinical studies underway in leukaemia and lymphoma are investigating rapalogs (sirolimus, everolimus, temsirolimus, ridaforolimus) as single agents, or in combination with standard chemotherapeutic agents, or other targeted agents (Table 1).

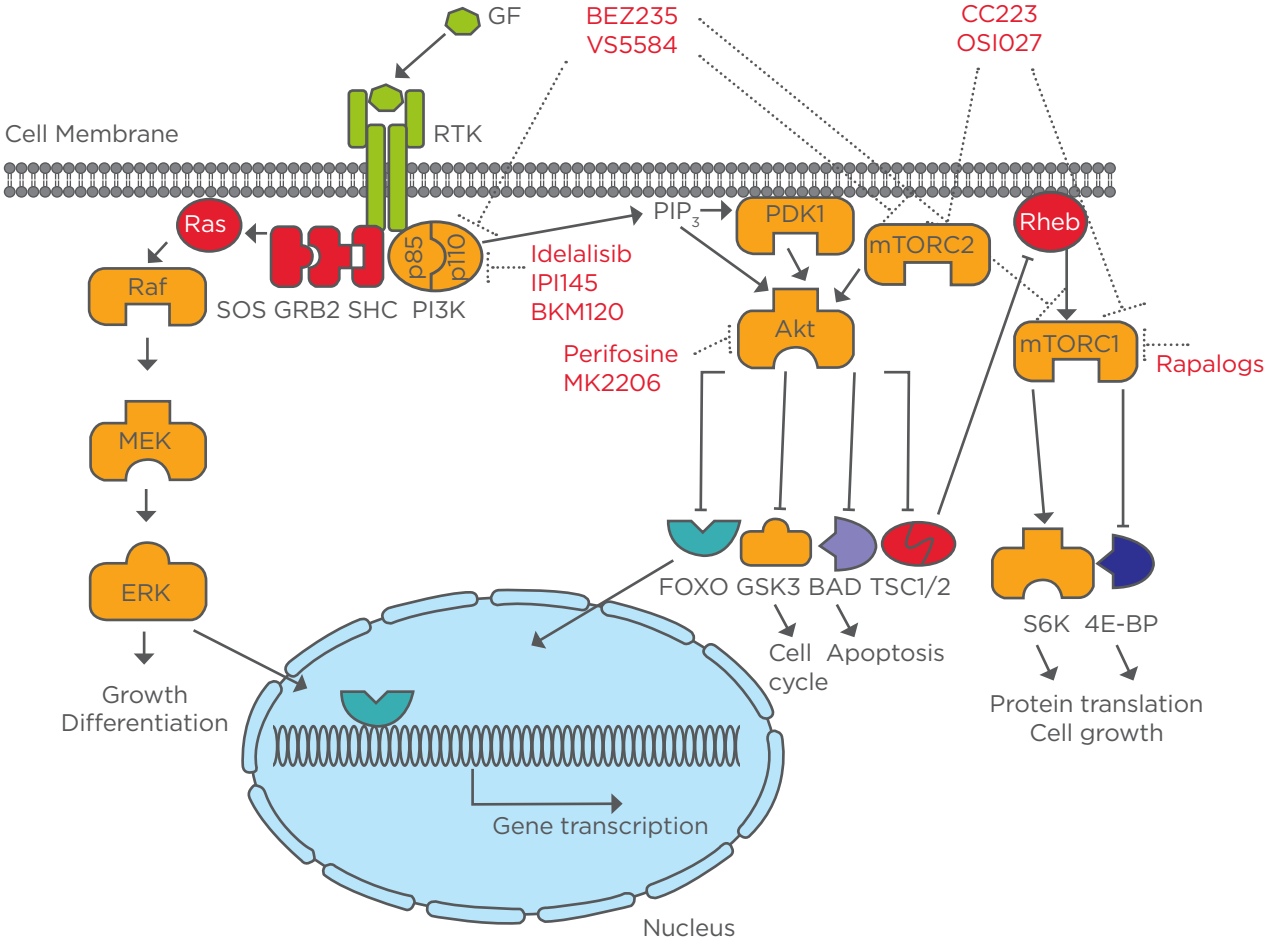

Figure 1: Schematic representation of the PI3K pathway, its regulation by growth factor (GF) binding to receptor tyrosine kinases (RTKs) and the main downstream mediators activated.

The main classes of targeted drugs (Akt inhibitors, PI3K inhibitors, PI3K/mTOR inhibitors, mTOR kinase inhibitors, and allosteric mTOR inhibitors/rapalogs) are also depicted.

PI3K: phosphoinositide 3-kinase; mTOR: mechanistic target of rapamycin; Akt: murine thymoma viral oncogene homolog; mTORC1: rapamycin complex 1; mTORC2: rapamycin complex 2; Rheb: Ras homologue enriched in the brain; 4E-BP: 4E binding protein; S6K: S6 kinase; SOS: son of sevenless; GRB2: growth factor receptor-bound protein 2; SHC: SH2-containing proteins; ERK: extracellular-signal-regulated kinase; Ras: rat sarcoma; MEK: mitogen-activated protein kinase; FOXO: forkhead box subgroup O; GSK3: glycogen synthase kinase 3; BAD: Bcl-2-associated death promoter; TSC1/2: tuberous sclerosis complex Type 1/2; PDK1: phosphoinositide-dependent kinase-1.

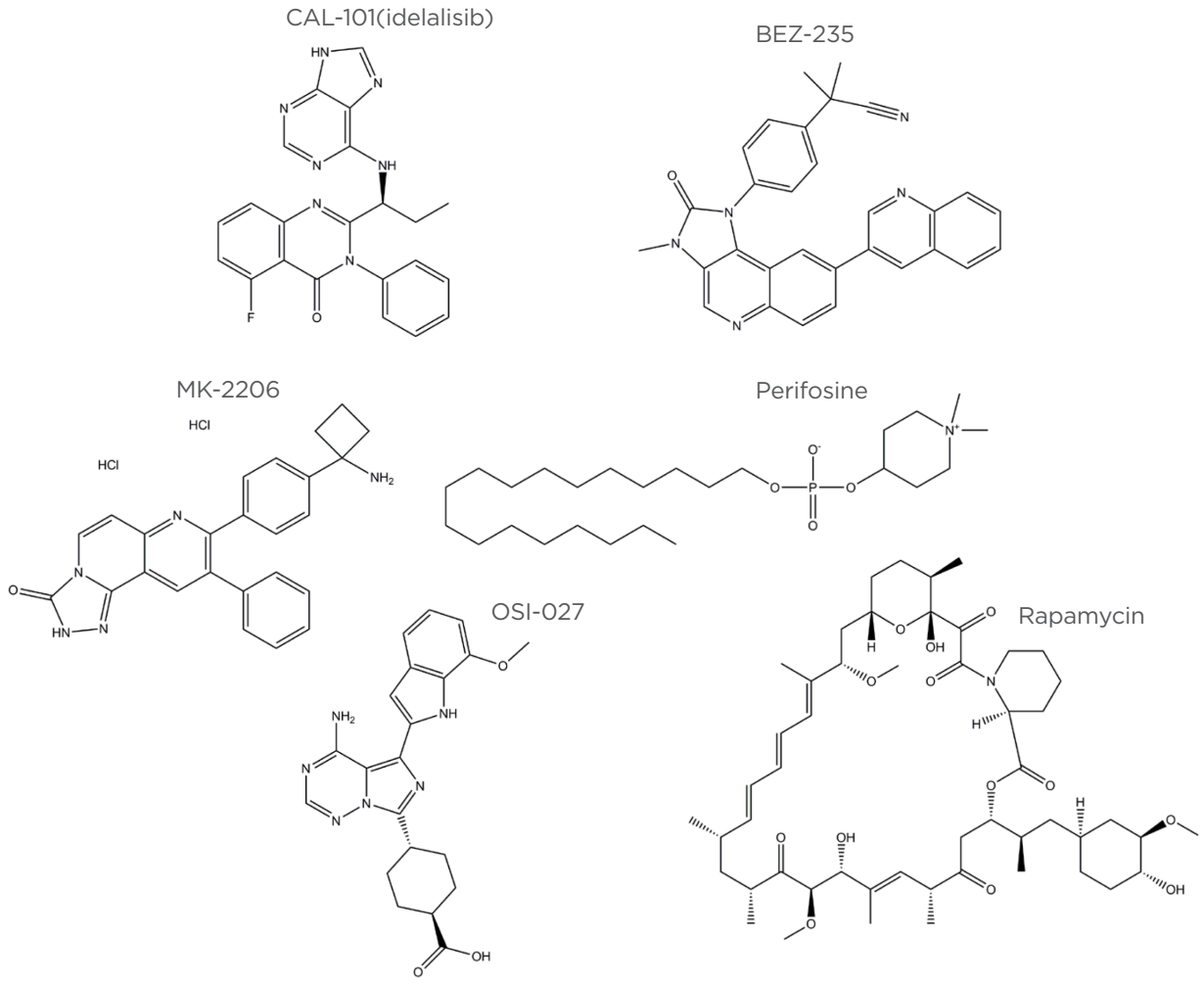

Figure 2: Chemical structures of selected PI3K/Akt/mTOR pathway inhibitors.
The p110δ inhibitor CAL-101 (idelalisib), the PI3K/mTOR inhibitor BEZ-235, the Akt inhibitors MK-2206 and perifosine, as well as the mTOR inhibitors OSI-027 and rapamycin are presented.
PI3K: phosphoinositide 3-kinase; Akt: v-akt murine thymoma viral oncogene homolog; mTOR: mechanistic target of rapamycin.

Temsirolimus (Torisel®) is approved for the treatment of relapsed and/or refractory mantle cell lymphoma (MCL) in the European Union and several other countries outside the USA. In a Phase III trial, temsirolimus significantly improved progression-free survival and objective response rate compared with other therapeutic regimens in patients with relapsed or refractory MCL.[53] In a Phase II trial in relapsed or refractory MCL, the combination of temsirolimus and rituximab produced an ORR of 59%.[54] Everolimus was also found to be active in relapsed or refractory MCL in a Phase II clinical trial.[55]

In addition to rapalogs, mTOR can be targeted by kinase inhibitors that have the advantage of inhibiting both mTORC1 and mTORC2. The mTOR kinase inhibitor OSI-027 was reported to be active in pre-clinical studies in BCR-ABL-expressing CML cells, AML, ALL, and lymphoma.[56-58] OSI-027 and CC223 are currently undergoing Phase I clinical testing in lymphoma, together with other solid tumours (Table 1). The Akt inhibitor MK-2206 was evaluated in a Phase II clinical trial in AML, but had only limited activity as a single agent, although it displayed anti-leukemic activity in a pre-clinical setting.[59] Further clinical trials are ongoing with this agent in lymphoma and leukaemia (Table 1). Perifosine is another Akt inhibitor that has been evaluated in pre-clinical and clinical studies in leukaemia and lymphoma.[60-62] A Phase II study in CLL found limited responses, but these did not correlate with impaired Akt phosphorylation, suggesting Akt-independent effects of perifosine.[63] Feedback and feedforward loops are known to occur between PI3K, mTORC1, mTORC2, and Akt.

Table 1: Overview of current clinical trials with selected PI3K/Akt/mTOR pathway inhibitors in leukaemia and lymphoma (data from http://clinicaltrials.gov/).

ID ClinicalTrials.gov	Phase	Drug(s)	Target(s)	Disease
NCT01756118	I	BEZ-235 single agent	PI3K + mTOR	acute leukaemia
NCT01991938	I	VS-5584 single agent	PI3K + mTOR	lymphoma
NCT01396499	I	BKM-120 single agent	Class I PI3K	leukaemia
NCT02049541	I	BKM-120 + rituximab	Class I PI3K	B cell lymphoma
NCT01719250	pilot study	BKM-120 single agent	Class I PI3K	NHL
NCT01693614	II	BKM-120 single agent	Class I PI3K	lymphoma
NCT01476657	I	IPI-145 single agent	p110δ + p110γ	HM
NCT01871675	I	IPI-145 + bendamustine/rituximab	p110δ + p110γ	lymphoma, CLL
NCT02158091	Ib/II	IPI-145 + fludarabine/cyclophosphamide/rituximab	p110δ + p110γ	CLL
NCT01882803	II	IPI-145 single agent	p110δ + p110γ	NHL
NCT02049515	III	IPI-145 + ofatumumab	p110δ + p110γ	CLL, SLL
NCT02004522	III	IPI-145 + ofatumumab	p110δ + p110γ	CLL, SLL
NCT02204982	III	IPI-145 + rituximab	p110δ + p110γ	lymphoma
NCT01088048	I	idelalisib + chemotherapy/immunomodulatory/anti-CD20	p110δ	lymphoma, CLL
NCT01090414	I	idelalisib single agent	p110δ	CLL, NHL
NCT01644799	I	idelalisib + lenalidomide	p110δ	follicular lymphoma
NCT01306643	I/II	idelalisib single agent	p110δ	NHL
NCT01838434	I/II	idelalisib + lenalidomide	p110δ	lymphoma (MCL)
NCT01393106	II	idelalisib single agent	p110δ	HL
NCT01203930	II	idelalisib + rituximab	p110δ	CLL, SLL
NCT01796470	II	idelalisib + GS-9973	p110δ	lymphoma, CLL
NCT02135133	II	idelalisib + ofatumumab	p110δ	CLL, SLL
NCT02044822	II	idelalisib + rituximab	p110δ	CLL (17p del)
NCT01569295	III	idelalisib + bendamustine/rituximab	p110δ	CLL
NCT01539291	III	idelalisib single agent	p110δ	CLL
NCT01732926	III	idelalisib + bendamustine/rituximab	p110δ	NHL
NCT01732913	III	idelalisib + rituximab	p110δ	NHL
NCT01659021	III	idelalisib + ofatumumab	p110δ	CLL
NCT01980888	III	idelalisib + bendamustine/rituximab	p110δ	CLL
NCT01658007	pilot study	sirolimus + multiagent chemotherapy	mTOR	leukaemia, lymphoma
NCT00874562		rapamycin + corticosteroid	mTOR	ALL
NCT01154439	I	everolimus + multiagent chemotherapy	mTOR	leukaemia
NCT01403415	I	temsirolimus + dexamethasone/ mitoxantrone/vinc/pegaspargase	mTOR	leukaemia/lymphoma
NCT01523977	I	everolimus + chemotherapy	mTOR	paediatric ALL
NCT00671112	I	everolimus + bortezomib	mTOR	lymphoma
NCT02240719	I	everolimus + bendamustine	mTOR	leukaemia, lymphoma
NCT00819546	I	everolimus + PKC412	mTOR	AML, MDS
NCT01902160	I	temsirolimus + brentuximab vedotin	mTOR	HL
NCT01535989	I	temsirolimus + inotuzumab ozogamicin	mTOR	B cell lymphoma
NCT01169532	I	ridaforolimus + vorinostat	mTOR	lymphoma

Table 1 continued.

ID ClinicalTrials.gov	Phase	Drug(s)	Target(s)	Disease
NCT00968253	I,II	everolimus + chemotherapy	mTOR	ALL
NCT00935792	I,II	everolimus + alemtuzumab	mTOR	lymphocytic leukaemia
NCT00918333	I,II	everolimus + panobinostat	mTOR	leukaemia, lymphoma
NCT02109744	I,II	rapamycin + decitabine	mTOR	AML
NCT01075321	I,II	everolimus + lenalidomide	mTOR	lymphoma
NCT01076543	I,II	temsirolimus + lenalidomide	mTOR	lymphoma
NCT01381692	I,II	temsirolimus + bortezomib/rituximab/ dexamethasone	mTOR	lymphoma
NCT01389427	I,II	temsirolimus + rituximab/chemotherapy	mTOR	MCL
NCT01198665	I,II	everolimus + chemotherapy	mTOR	lymphoma
NCT01567475	I,II	everolimus + rituximab	mTOR	NHL
NCT01078142	I,II	temsirolimus + rituximab, bendamustine	mTOR	lymphoma
NCT00474929	I,II	everolimus + sorafenib	mTOR	lymphoma
NCT01453504	I,II	everolimus + DHAP	mTOR	HL
NCT01854606	Ib/II	everolimus + AEB071	mTOR	B cell lymphoma
NCT00634244	II	sirolimus + combination chemotherapy	mTOR	AML
NCT01611116	II	temsirolimus + standard therapy	mTOR	AML
NCT01869114	II	sirolimus + azacitidine	mTOR	AML, MDS
NCT00838955	II	temsirolimus single agent	mTOR	HL
NCT01022996	II	everolimus single agent	mTOR	HL
NCT01843998	II	sirolimus single agent	mTOR	cut T cell lymphoma
NCT01665768	II	everolimus + rituximab	mTOR	lymphoma
NCT01653067	II	temsirolimus + rituximab, DHAP	mTOR	B cell lymphoma
NCT00942747	II	temsirolimus single agent	mTOR	lymphoma (CNS)
NCT01637090	II	everolimus single agent	mTOR	cut T cell lymphoma
NCT01281917	II	temsirolimus + velcade	mTOR	NHL
NCT00978432	II	everolimus + LBH589	mTOR	B cell lymphoma
NCT00790036	III	everolimus single agent	mTOR	B cell lymphoma
NCT01646021	III	temsirolimus (versus ibrutinib) single agent	mTOR	MCL
NCT00700258	IV	temsirolimus + sunitinib	mTOR	MCL
NCT01180049	IV	temsirolimus single agent	mTOR	NHL
NCT00698243	I	OSI-027 single agent	mTOR	lymphoma (+ other)
NCT01177397	I,II	CC-223 single agent	mTOR	B cell lymphoma
NCT01369849	I/II	MK-2206 + bendamustine/rituximab	Akt	CLL, SLL
NCT01258998	II	MK-2206 single agent	Akt	lymphoma
NCT01253447	II	MK-2206 single agent	Akt	AML
NCT01481129	II	MK-2206 single agent	Akt	B cell lymphoma

mTOR: mechanistic target of rapamycin; PI3K: phosphoinositide 3-kinase; NHL: non-Hodgkin's lymphoma; CLL: chronic lymphocytic leukaemia; MCL: mantle cell lymphoma; ALL: acute lymphocytic leukaemia; HL: Hodgkin's lymphoma; Akt: v-akt murine thymoma viral oncogene homolog; SLL: small lymphocytic leukaemia; MDS: myelodysplastic syndrome; HM: haematological malignancy; CNS: central nervous system; AML: acute myeloid leukaemia.

These loops explain that synergy between selected kinase inhibitors (such as JAK2 inhibitors) and PI3K inhibitors, especially pan-class I PI3K inhibitors, has been reported in myeloid malignancies, including myeloproliferative neoplasms.[64,65] These combinations may be further studied in other haematological malignancies, where these regulatory loops are relevant.

CONCLUSION AND OUTLOOK

The approval of the first PI3K inhibitor for CLL and B cell NHL in 2014 strongly supports the further development of PI3K pathway inhibitors in leukaemia and lymphoma. The most advanced drugs are p110δ PI3K inhibitors (idelalisib) and rapalogs (temsirolimus). Multiple clinical trials are underway with these agents in haematological malignancies and it is likely that further drugs will be approved in different indications in the near future. There are different possible ways to optimise the use of these agents in the future, including the development of predictive biomarkers for patient selection, the design of additional combinatorial approaches involving PI3K inhibitors and other drugs (targeted agents or standard chemotherapy), and the elucidation of potential mechanisms of resistance.

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